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*By* Manisha Nallani

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# Unmasking phenytoin toxicity: a case of acute neuro-hepatic crisis

Manisha Nallani,Sarmini Varatharajan, Anthony Joseph Britto, Priyadarshini Varadaraj
Department of General Medicine, Saveetha Medical College and Hospital, SIMATS Deemed University, Chennai, Tamil Nadu, India

Manisha Nallani **ORCID ID:** 0009-0001-7524-1007
Sarmini Varatharajan **ORCID ID:** 0009-0006-4647-7105
Anthony Joseph Britto **ORCID ID:** 0009-0008-7485-1795
Priyadarshini Varadaraj **ORCID ID:** 0001-0001-5293-5447

*Corresponding author:*
Manisha Nallani
*E-mail:* manishanallani22@gmail.com

**Abstract**

Phenytoin remains a widely prescribed anti-epileptic, particularly in low- and middle-income countries, owing to its affordability. However, its narrow therapeutic index and unpredictable metabolism predispose patients to toxicity. We report a case of a 44-year-old woman who, within two months of initiating phenytoin therapy, developed progressive unsteadiness, dysarthria, limb weakness, and encephalopathy. Investigations revealed markedly elevated serum phenytoin levels (40 mg/dL), significant hyperammonemia, and hepatocellular injury with raised transaminases. Early recognition of phenytoin-induced toxicity, prompt drug withdrawal, and supportive management, including lactulose and substitution with levetiracetam, led to full neurological and biochemical recovery over three weeks. This case highlights the importance of therapeutic drug monitoring, timely recognition of drug-induced neuro-hepatic dysfunction, and awareness of phenytoin's toxic potential, particularly within the initial months of therapy.

**Keywords:** antiepileptic drug adverse effects, therapeutic drug monitoring, hyperammonemic encephalopathy, drug-induced ataxia, idiosyncratic drug reaction

**Ethical Considerations**

Informed consent was obtained from the patient for the publication of clinical details and images, ensuring compliance with bioethical research regulations.

**Conflict of Interest:** None to declare

## Introduction

Phenytoin was introduced to clinical practice in 1938 [1] and continues to be widely used as an antiepileptic agent due to its availability and cost-effectiveness. However, its use is limited by a narrow therapeutic index and non-linear pharmacokinetics, predisposing patients to toxicity, particularly with prolonged therapy, drug interactions, or metabolic variability. Neurological manifestations of phenytoin toxicity typically include ataxia, dysarthria, nystagmus, and encephalopathy. Although hepatotoxicity is rare, it can be severe and is frequently underrecognized. We report a case of combined phenytoin-induced neurotoxicity and hepatotoxicity, and discuss the differential diagnoses and clinical implications.

## Case Presentation

A 44-year-old woman presented with a two-week history of progressive unsteadiness of gait, confusion and slurred speech. Her family reported that she had been increasingly disoriented, exhibiting inappropriate responses, forgetfulness, and occasional irrelevant speech. She was unable to perform daily tasks independently and required assistance for ambulation due to unsteadiness and swaying while walking. There were no recent seizures or head trauma reported.

She had been diagnosed with seizure disorder two months earlier and was initiated on oral phenytoin at a dose of 100 mg in the morning and 200 mg at night.

On initial neurological examination, she was conscious but disoriented to time, place, and person. Vital parameters were stable. Cerebellar signs were evident, including scanning speech, truncal and limb ataxia, and horizontal nystagmus.

Motor examination revealed symmetrical quadriparesis with Medical Research Council grade 3/5 power in all four limbs. Deep tendon reflexes were brisk, and bilateral extensor plantar responses (Babinski positive) were noted. Sensory modalities were intact.

Serum phenytoin levels were markedly elevated at 40 mg/dL (therapeutic range: 10–20 mg/dL), confirming drug toxicity. Liver function tests showed elevated AST (201 U/L) and ALT (223 U/L), while serum ammonia was raised at 184 µg/dL, suggestive of hyperammonemia-associated encephalopathy. Other laboratory investigations, including complete blood count, serum electrolytes, renal function tests, and serum albumin, were within normal limits. Viral hepatitis serologies were negative.
Neuroimaging with non-contrast CT brain was unremarkable, while MRI revealed chronic thrombosis with incomplete recanalization of the superior sagittal, left transverse, and left sigmoid sinuses. Serum creatine phosphokinase levels were normal, effectively ruling out a concurrent myopathy.

Phenytoin was withheld upon confirmation of supratherapeutic levels. Following which oral levetiracetam was initiated as an alternative antiepileptic. With supportive care, the patient showed marked clinical improvement in her neurological signs and liver function parameters over a three-week period.

**Differential Diagnosis**

In this patient presenting with subacute cerebellar ataxia, encephalopathy, and hepatic dysfunction, a systematic differential diagnosis was considered. Acute viral hepatitis was excluded based on negative serologies and absence of systemic features. Wernicke's encephalopathy was unlikely given the absence of ophthalmoplegia, amnesia, or nutritional deficiency. Although cerebral venous sinus thrombosis was noted on MRI, its chronic nature without acute infarcts made it an improbable cause of the current symptoms. Autoimmune encephalitis was considered but excluded in view of the lack of seizures, psychiatric manifestations, or CSF abnormalities. Wilson's disease was deemed unlikely based on age, clinical context, and absence of supporting laboratory or ophthalmic findings. Hyperammonemia-induced encephalopathy was contributory but likely secondary to drug-induced hepatic dysfunction. The markedly elevated serum phenytoin levels, along with rapid clinical and biochemical improvement following drug withdrawal, confirmed the diagnosis of phenytoin-induced neurotoxicity with hepatotoxicity.

**Discussion**

Phenytoin toxicity is characterized by dose-dependent neurological symptoms, most commonly ataxia, nystagmus, and dysarthria. Encephalopathy can occur at higher serum levels or in predisposed individuals, particularly with impaired metabolism. Our patient had serum levels twice the upper therapeutic limit, correlating with her cerebellar signs and altered mental status. Notably, she also exhibited signs of hepatic injury, a rare but serious complication of phenytoin.

A recent case report by Khadela et al. documented a 16-year-old patient who developed phenytoin-induced ataxia with toxic serum drug levels of 40 μg/mL, presenting with giddiness, vomiting, and MRI changes suggestive of periventricular leukomalacia. Similar to our patient, the neurological symptoms correlated with elevated phenytoin levels and showed clear clinical improvement following withdrawal of the drug and adjustment of antiepileptic therapy. While Khadela et al.'s report primarily focused on isolated neurotoxicity, our case additionally involved hepatic dysfunction and hyperammonemia, broadening the recognized spectrum of phenytoin-related adverse effects. Despite these differences, both cases emphasize the importance of timely identification of toxicity and demonstrate favorable outcomes with prompt drug cessation and supportive care. [2]

A case series by Arora et al. highlights the diverse and cumulative neurotoxic manifestations of long-term phenytoin therapy, including ataxia, dysarthria, cerebellar atrophy, and gum hypertrophy, predominantly in chronic users over years of therapy. In contrast, our patient developed acute phenytoin-induced neurological and hepatic toxicity within a relatively short duration, with serum phenytoin levels in the toxic range. While Arora et al. emphasize irreversible structural cerebellar damage observed through neuroimaging in chronic toxicity, our case underscores the importance of early identification of reversible neurological symptoms such as ataxia and altered sensorium, alongside hepatic dysfunction, which significantly improved after prompt withdrawal of phenytoin. Both reports advocate for vigilance in monitoring phenytoin levels and adverse effects, with our case reinforcing that even early or acute toxicity can produce serious yet reversible outcomes if recognized timely. Together, these cases advocate for stricter therapeutic drug monitoring protocols and early clinical suspicion to mitigate both acute and chronic toxicities associated with phenytoin. [3]

In another case presented by Bhavsar et al. [1], a 64-year-old woman on phenytoin developed hepatotoxicity characterised by mild transaminitis and cholestatic features, confirmed histologically and managed successfully with drug cessation. Notably, the patient exhibited predominantly hepatic symptoms without overt neurotoxicity or encephalopathy. In contrast, our patient not only demonstrated significant hepatotoxicity with AST and ALT levels exceeding 200 U/L but also developed classical neurotoxic manifestations, including cerebellar signs, encephalopathy, and hyperammonemia, at a markedly elevated phenytoin level of 40 mg/dL. Unlike the Bhavsar et al. case, imaging in our patient revealed chronic cerebral venous sinus thrombosis; however, its chronicity and absence of acute infarcts rendered it an unlikely contributor to the acute presentation. Both cases underscore the importance of recognising phenytoin-induced hepatic injury as a diagnosis of exclusion, with improvement following withdrawal of the drug. However, our case highlights that at toxic serum levels, phenytoin can precipitate a dual insult, both hepatocellular dysfunction and central neurotoxicity, which can be life-threatening if unrecognised. These cases collectively reinforce the need for regular therapeutic drug monitoring and prompt discontinuation upon suspicion of drug-induced liver injury. [4]

Robertson et al. reported a case on an elderly gentleman who developed classic cerebellar signs and central ataxia while on chronic phenytoin therapy, with measured total phenytoin levels within range. However, concurrent hypoalbuminemia and hyperbilirubinemia increased the free, pharmacologically active fraction of phenytoin, precipitating toxicity. In contrast, our patient presented with overtly elevated total phenytoin levels, accompanied by both neurological and hepatic dysfunction. Unlike the Robertson case, where toxicity was unmasked by altered protein binding, our case was primarily dose-dependent, reflecting phenytoin's narrow therapeutic index and non-linear kinetics. Importantly, both cases highlight the potential for toxicity in vulnerable metabolic settings, emphasizing that clinical judgment should supersede reliance on total drug levels alone. This is particularly crucial when hypoalbuminemia, hepatic dysfunction, or drug interactions are present, warranting either free phenytoin level estimation or empiric dose adjustment when toxicity is suspected.[5]

**Conclusion**

Phenytoin, despite being one of the oldest antiepileptic agents in clinical practice, continues to be widely prescribed in resource-limited and developing settings due to its affordability and proven efficacy. However, its use is constrained by a narrow therapeutic index and non-linear pharmacokinetics, making it prone to toxicity, especially with prolonged therapy, drug interactions, metabolic variability, or hepatic dysfunction. Neurological manifestations of phenytoin toxicity typically include ataxia, dysarthria, nystagmus, and encephalopathy, while hepatotoxicity, though rare, can range from mild transaminitis to life-threatening acute liver failure.

Our case adds to the limited literature describing combined neurotoxicity and hepatotoxicity from phenytoin, presenting within a relatively short period of use. The patient exhibited classical cerebellar signs, encephalopathy, hyperammonemia, and significant hepatocellular enzyme elevation, with markedly elevated serum phenytoin levels. Prompt recognition, withdrawal of phenytoin, and initiation of levetiracetam resulted in rapid clinical and biochemical improvement, emphasizing the reversibility of early toxicity.

Comparatively, literature documents isolated neurotoxicity or hepatotoxicity in most cases. For instance, Khadela et al. reported isolated phenytoin-induced ataxia at toxic serum levels, with favorable outcomes upon discontinuation. Arora et al. described long-term cumulative neurotoxic effects such as cerebellar atrophy and irreversible deficits, typically following years of therapy. In contrast, our case underscores that even acute toxicity within a short duration can be severe and life-threatening if not identified early.

Similarly, Bhavsar et al. presented a case of phenytoin-induced hepatotoxicity manifesting as mild transaminitis and cholestatic features, without overt neurological involvement. Our case extends these observations, highlighting that phenytoin at toxic levels can cause a dual systemic insult, neurotoxicity and hepatotoxicity simultaneously, necessitating a high index of suspicion.

Moreover, Robertson et al. demonstrated that toxicity may occur even with total phenytoin levels within the therapeutic range, due to alterations in protein binding secondary to hypoalbuminemia and hyperbilirubinemia. This reinforces the clinical principle that symptomatology must take precedence over laboratory values alone, and where feasible, free phenytoin levels should be considered, particularly in patients with hepatic dysfunction or protein-binding abnormalities.

In conclusion, this case emphasizes the importance of regular therapeutic drug monitoring, early clinical recognition of toxicity, and prompt drug cessation. It also advocates for revisiting clinical protocols to ensure patient safety when prescribing phenytoin, especially in susceptible individuals, to prevent potentially fatal outcomes.

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